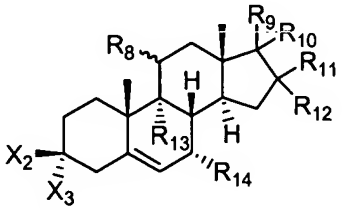
REMARKS

In response to the office action of March 19, 2003, the claims have been amended to overcome the rejection under 35 U.S.C. § 112. Any potential ambiguity as to the various definitions of "R" has been eliminated by using R_p where R = alkyl; R_q where R = H or alkyl; R_s, R_t, R_u and R_v where R = H, alkyl, or aryl; R_w, R_x, and R_y where R = alkyl or aryl; and R_z where R = aryl. Claims 1, 27, and 35 have been amended to delete the periods that were in the middle of the claims and replace them with commas. Claims 13 and 33 have been amended to correct typographical errors such that the integer "m" is properly defined. Claims 4, 9, 16, 24, 43, 45, 52, 54, 56, and 63 have been amended to correct certain informalities in the Markush claim language. No change in the scope of the claims is intended by any of the foregoing amendments.

The instant invention is a breakthrough in the method of ketone-catalyzed β-selective epoxidation of Δ^5 unsaturated steroids, and in particular a method of producing 5,6-β steroid epoxides. Ketone catalyzed epoxidation reactions are unpredictable as to the ratio of β to α isomers produced. Applicants have found that for epoxidation of Δ^5 unsaturated steroids, the use of ketones of formula I, or the corresponding dioxiranes of formula VI, will result in mostly 5,6-β steroid epoxides. This discovery is recited in independent claims 1 and 26, respectively. Applicants also have discovered that Δ^5 unsaturated steroids that specifically incorporate 3-α-substituents will produce mostly 5,6-β steroid epoxides when the epoxidation reaction is carried out with a ketone or dioxirane catalyst, as recited in independent claims 12 and 32. Finally, applicants herein have found that for epoxidation of compounds of formula XI, ketones of formula XII will give good β selectivity, as recited in independent claim 42; and further that for

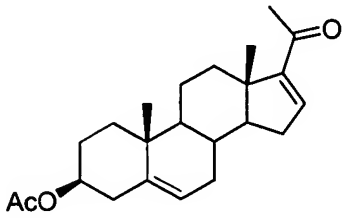
epoxidation of compounds of formula XIII, which specifically incorporate 3-α-substituents, ketones XIV, XV, XVI and XVII will give high β selectivities, as recited in independent claim 53. See Tables 1-3 of the specification. Prior to the instant invention, there has been no literature report of such high β-selectivity achieved in the epoxidation of Δ^5 unsaturated steroids.

The rejection of the claims under 35 U.S.C. § 103 as obvious over Bovicelli et al., Cicala et al., Holland et al., and Yang et al., in combination, is respectfully traversed. The instant claims recite a method for, inter alia, the epoxidation of structure XI:



XI

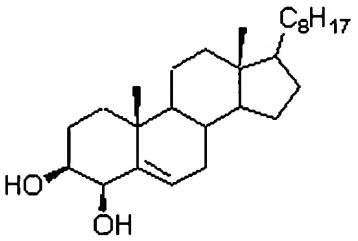
The Bovicelli reference teaches the epoxidation of a compound of the following structure.



This structure is a Δ^5-unsaturated steroid, as recited in independent claims 1 and 26, but it is not a 3α-substituted steroid of independent claims 12 and 32, nor is it the steroid of formula XI of claim 42 or steroid XIII of claim 53. The dioxirane used was dimethyldioxirane, which is a dioxirane of formula IX, recited in claim 35, not the dioxirane corresponding to formula VI of claim 26. The instant application does not

claim the use of a ketone of formula IX with a 3β-substituted steroid, as taught by Bovicelli, and indeed, Bovicelli achieves a β/α-epoxide ratio of only 3:2, which does not compare favorably with the β/α-epoxide ratios reported in Table 2 of the instant application. Nor is there any teaching or suggestion in the Bovicelli reference that certain specific dioxiranes, namely those of formulae VII, VIII, IX, and X, would yield a substantially higher β/α-epoxide ratio when used in the epoxidation of a 3α-substituted steroid, as taught and claimed in the instant application.

The Cicala reference is directed to the epoxidation of a structurally similar but chemically distinct substrate, namely, allylic alcohols. In such structures, the 4-β-hydroxy group is essential to achieving β-selectivity. Cicala teaches the epoxidation of:



Cicala's substrate

It can be seen from a comparison of the applicants' structure II and the Cicala substrate that the Cicala structure includes an extra hydroxyl group on the carbon atom in the 4-beta position adjacent the double bond. The presence of this hydroxyl group is significant in terms of the Cicala epoxidation reaction. The Cicala structure does not have a 3α substituent and therefore does not fall within the scope of independent claims 12 and 32, nor does it fall within the structure XI of claim 42 or structure XIII of claim 53, because the 4-β hydroxy group is not present in the substrates recited in those claims. To the extent that the Cicala structure falls within the general category of Δ^5 unsaturated steroids of claims 1 and 26, Cicala does not teach or suggest the use of ketone I of claim

1 or dioxirane VI of claim 26. The applicants herein have achieved β selectivity in epoxidation reactions of compounds not having the 4-β-hydroxy group, and surprisingly have achieved much higher β/α ratios.

Holland et al. teach the epoxidation of epicholesterol, but do not teach the use of either ketones or dioxiranes in such a reaction, nor does the reference teach that the use of certain ketones or dioxiranes could greatly increase the β-selectivity of the epoxidation.

The Yang references disclose the use of ketone catalysts in the epoxidation of olefins, but do not teach or suggest that such olefins could be useful in the epoxidation of Δ^5 unsaturated steroids, either with or without 3α-substituents, nor do these references teach or suggest that the use of certain ketones or dioxiranes could greatly increase the β-selectivity of the epoxidation.

Applicants respectfully take exception to the Examiner's statement that "The claimed invention is a process for the production of predominantly 5,6-epoxides from the corresponding 5-ene steroid derivative in the presence of a ketone and an oxidant or the intermediate product thereof, i.e. a dioxirane." Rather, the applicants' invention, as recited in the claims, is a process for the production of 5,6 β epoxides from the corresponding 5-ene steroid derivative, and in particular certain such steroid derivatives with 3α substituents, in the presence of certain selected ketones or their corresponding dioxiranes. Not all ketones and their corresponding dioxiranes will react with any and all 5-ene steroid derivatives to produce the desired β-selectivity. The instant invention relates to the selection of the particular ketones and dioxiranes and the particular steroid compounds that will produce this highly desirable result. Further, given the

unpredictable nature of these reactions, the β-selectivity achieved with the methods of the instant invention could not have been predicted.

The advantage of the instant invention is significant because it means that users of the instant invention can achieve a greater proportion of the desired β product, which brings the benefit of more desired product per quantity of starting material, and less time spent in separating the 5,6-β epoxides from the 5,6-α epoxides. The invention is non-obvious for the further reason that the 5,6-β-epoxides have not been the subject of extensive research in the literature because of the difficulty in their preparation. The instant invention overcomes those previous difficulties. In fact, some of the compounds reported in the instant application are new compounds. See, Yang, et al., Chem. Eur. J. 2000, vol. 6, pages 3517-3521, compounds 8a and 8b, 11a and 11b. Applicants acknowledge that the two Yang references cited by the Examiner taught ketone-catalyzed epoxidation, but point out that the substrates in those references were limited to unfunctionalized olefins.

Thus, it is immaterial whether it would have been obvious to use a dioxirane derivative in the epoxidation of olefinic compounds; or whether there was a reasonable expectation that any 5-ene steroid derivative, including 3α-substituted-5-ene isomers, would undergo epoxidation with the production of the corresponding 5,6-epoxy compounds; or that dioxirane derivatives would be produced in situ by the reaction of a ketone and an oxidant. None of these factors goes to the selection of particular steroids and/or particular ketones or dioxiranes to achieve epoxides of a desired stereoselectivity. Such unexpected stereoselectivity is not the result of "optimum epoxidation properties," but of the careful selection of reaction components in ways heretofore not understood in

the art. Such careful selection goes beyond the "optimum reaction conditions" that would normally be expected of a skilled artisan. For example, none of the references teaches that the presence of a substituent in the 3α position influences the stereochemistry of the oxygen atom at the 5,6 position in the resulting epoxide.

For the foregoing reasons, it is believed that each of the grounds of rejection has been overcome, and a Notice of Allowance is respectfully requested.

Respectfully submitted,

Sandra B. Weiss

Sandra B. Weiss
Reg. No. 30,814
JONES DAY
77 West Wacker
Chicago, Illinois 60601-1692
(312) 782-3939